generous, you've to get there.

And again, I'm not quite sure that we've accomplished that as we've discussed.

CHAIRMAN BORER: Okay. Do we have information about age?

DR. LIPICKY: Do you want to divide the effect size up?

CHAIRMAN BORER: Do I?

DR. LIPICKY: And then figure out what --

CHAIRMAN BORER: No.

DR. LIPICKY: Well, why did you ask the question then?

CHAIRMAN BORER: I asked this question because somebody needed a clarification on the panel.

DR. LIPICKY: But he knows the answer. The effect size is ten meters. How many ways do you want to divide that up?

CHAIRMAN BORER: Well, wait. All we want to know is there --

DR. LIPICKY: You're not going to get an answer to the question. So don't spend time trying to answer it.

CHAIRMAN BORER: Give us a yes or a no then.

Okay. That's a no.

DR. LIPICKY: There are no data that are pertinent to the question, not no effect.

CHAIRMAN BORER: One, point, two, how, if at all, did the following exaggerate the apparent drug effects, withdrawals, rules, missing data, others?

We've heard a great deal about that. I don't know if we have to repeat it all. I think Tom gave that analysis unless anybody has anything else to say about it.

One, point, three, the prospective analysis plan included rules for handling the data from subjects who withdrew prior to final assessment. Other rules were explored by the sponsor and by the reviewers. Was the prospective rule the best way to assess the effect of size or appropriately conservative?

I think we've heard a good deal about that as well. Are there any other comments besides the analysis Tom gave?

Ray, do you need any more guidance than what you heard? No.

One, point, four, if these were the only data available, only available data, would this result have been close enough to have represented substantial evidence of effectiveness? If so, what should have been the prospective standard for a two-study development program?

I think that question has more wide ranging implications that merely this study. So I think we ought to hear some comments about that.

Why don't we start on the other side at this time with Michael Artman.

DR. ARTMAN: Well, this is tough, and I think this is really at the heart of the issue. I guess my gut sense is that, yeah, it's close enough. I mean, it's suggestive that there is some treatment effect.

Now, whether that treatment effect is clinically meaningful or not, we could spend the next three day arguing, I think. So I believe that the data do show a treatment effect.

CHAIRMAN BORER: Can I just ask, Ray, for a clarification? One, point, four begins with the clause or phrase, "If these were the only available data." Which data are we talking about?

DR. LIPICKY: I think the way you ought to look at it is the prospectively defined endpoint, the prospectively defined rules.

CHAIRMAN BORER: Oh, okay.

DR. LIPICKY: Because those are, in fact, what Bob Temple said were close sort of.

CHAIRMAN BORER: Okay.

DR. LIPICKY: And what everybody -- I think everybody else was talking -- well, so the prospective endpoint, the prospective rules, they didn't make it. The question sort of is are we playing games with 049 or 050?

And that's what Bob Temple suggested, you know. Are we slaves to statistics, recognizing that two .05 trials usually means .00125. So, you know, everything here is an order of magnitude off.

So I think it's in that framework that this question is posed, and however, we're willing to

-- you know, you might come to the conclusion together that, you know, it didn't make the prospective rule, but it is close enough to say that it did because you're not a slave to p values.

DR. FLEMING: Jeff.

DR. LIPICKY: Or then you will be able to go farther and say, "Well, I concluded that it didn't make it here, but now I'm going to say something else tips it over even though what I said here in 1.4 isn't enough."

So this isn't the final answer.

CHAIRMAN BORER: Tom, did you want to comment on this issue for a second?

DR. FLEMING: Well, with the clarification that you've just provided, Ray, which if I follow what you said is if we say that the 04 and 05 trial data on the primary endpoint of six minute walk are the only data available, would this have been close enough, we missed the primary targets for strength of evidence.

It can well be argued that those were lenient in the sense that it was a two study, 01, when as you pointed out, usually we'd be going for .00125.

The study was targeting a 55 meter difference. It achieved a ten or 16 meter difference, and if the truth was anything close to a 55 meter difference, this study would have blown away any of the statistical criteria for significance even at the .00125 level.

And so the criteria that you would normally have anticipated of .00125, we didn't even come close to. The targeted criteria of .01, yeah, we're in that ballpark, but when you make some very appropriate recognitions of the bias with missingness, it's very controversial as to whether we're close.

CHAIRMAN BORER: Jeff, let's go back to the end here, and -- I'm sorry, Bob. Did you want to?

DR. TEMPLE: There's two parts to it. One part is if you believe those p values, if you didn't have to adjust or correct them, what would you think, but simultaneously you also have to deal with the points about possible exaggeration of the benefit that's suggested by potentially informative censoring, and those are two somewhat separable questions.

You might think that the p values, if

real, are close enough, but you don't trust them. That would lead to one conclusion.

You might conclude that informative censoring was probably not such a bad problem and, therefore, you do believe them. That could lead to a different, but you have to sort of think about those two things together, I think, to answer this question.

DR. KOCH: If I could make a comment relative --

CHAIRMAN BORER: Let's hold that just for the moment. We'll get through these questions, and --

DR. KOCH: Well, I wanted to help you with the effect size.

CHAIRMAN BORER: Well, let's wait just for a moment.

Dr. Anderson, did you have any comment about this? No.

Steve?

DR. NISSEN: Okay. So we don't want to be slaves to p values. So what does that mean? What it means to me is that you take everything in the context that it occurs in, and I must tell you that I have to

look at this differently than a drug that may be exposed to hundreds of thousands or millions of individuals.

This is an orphan disease. It's a disease in which people are really desperate for help, and I think that if you really want to not be a slave to a p value, then you try to look at the totality of the data in a situation that puts it into context.

DR. LIPICKY: In the next question, you can make that plea. In this one you're talking about the primary endpoint only.

DR. NISSEN: Okay.

DR. LIPICKY: Okay? You can make that plea in the next question.

DR. NISSEN: All right. Well, having said that, I guess my conclusion is that it is close enough.

CHAIRMAN BORER: Dr. Brem.

DR. BREM: I would pass on this comment.

CHAIRMAN BORER: I'd like to second the part of Steve's comment that relates to this question, that I think relates to this question, and that is

that we're told that this is a problem that affects maybe 50,000 people in the world, not a large number available for study, and what we want to know is are these results sufficiently consistent; the primary endpoint data, are they sufficient consistent so we believe them even if they didn't make it to the prospectively defined determination rules?

And I have to say in the context of the kinds of measures that were used, it's possible that they do. I mean, I'd want to see more, but I can't say that this is or it isn't. I think that it could be, and then we'll get to the next question and determine whether it is in the context.

Tom already spoke. JoAnn, did you have something to say about this?

DR. LINDENFELD: No, I would say that just standing alone this is not quite enough evidence.

DR. ARMSTRONG: I think the data is hypothesis generating, and the magnitude of the effect size does not convince me that we're close enough.

CHAIRMAN BORER: Alan?

DR. HIRSCH: I am not a slave to p values,

but since we're taking the scientific approach, it doesn't achieve its primary defined endpoint, but we'll come back to that in a minute.

CHAIRMAN BORER: Okay. Let's go on to 1.5, which we've been presaging here with these comments.

Six minute walk was the primary endpoint in these studies, but there were other measures of clinical benefit. Is it methodologically sound to consider those results in deciding if the development program was successful in distinguishing drug from placebo?

If it is reasonable to use secondary endpoints this way, we have a whole series of questions, which I think we're not going to be able to answer as precisely as they're written, but we can try.

Again, these have more wide ranging implications, the answers to these. So we'll open it up widely here, and let's start on the left-hand side.

Alan, 1.5.1, how close to winning on the primary endpoint do you need to be?

DR. HIRSCH: Thank you. I just thought I wasn't a slave to the p values. So the question is how much compassion do I have.

CHAIRMAN BORER: Right.

DR. HIRSCH: I don't know how to answer that. Let's circle down the aisle here and have a discussion about this. I don't know.

CHAIRMAN BORER: Okay. Paul.

DR. ARMSTRONG: Well, I would just reiterate that closeness without consideration of the magnitude of the effect that's close influences me strongly. So if I'm close on something that doesn't achieve a magnitude that was originally anticipated, then the other factors become less important.

If the magnitude is substantial, then they become very important, indeed.

CHAIRMAN BORER: JoAnn?

DR. LINDENFELD: Yeah, I'd echo what Paul said. I think that's an important issue. What's the magnitude of effect here?

And again, the larger the magnitude, the less close I might have to be.

DR. KOCH: Could I please try to make a comment on the magnitude?

CHAIRMAN BORER: I'd rather you don't for a moment, please. Let us continue our deliberations. At the end if we have a little bit of time, we'd be happy to hear any closing comments.

Tom.l

DR. FLEMING: There's a whole series of sub-issues here. Jeff, at this point should we just be answering the is it methodologically sound to consider other measures? Is that essentially what we're doing at this point?

CHAIRMAN BORER: Yeah.

DR. FLEMING: I mean, it certainly is. When one is looking at an overall application, one does need to look globally at benefit to risk, and that is certainly our guided and should be targeting what we had prespecified in order to avoid the incredible temptation of putting excess influence on those things that turned out to look better when you had a myriad of different ways of assessing benefit.

I might start off by again saying I

challenge the premise that we're close on the primary endpoint, first and foremost, from a clinical perspective. We targeted 55. We had ten. That's not close.

And I also challenge that we're close on statistical significance. So there's a premise here that I think is underlying this question that is relevant and can be challenged.

It is relevant to look at other measures, and when we look at those other measures -- and I'll be very brief because I had a chance to be more detailed before -- I see effects, but they do seem to be modest in the effects on symptoms. They are not consistent. There are some measures more impressive than others, and there are very clear safety issues that have to be weighed against those modest improvements in secondary endpoints.

DR. LIPICKY: Forgive me, Tom. You must have some feeling for what "close" means. You don't think this is close. What would close be?

DR. FLEMING: There are close in two ways. It's easier to say something is not close than to say

what actually would be close. If you target 55 and you have ten, I'm comfortable saying that's not close. When you look at significance levels and you're targeting .01, and sure, if you have .006 to .015, that's, you know, certainly from a statistical perspective, that's close, and clearly it warrants looking at secondary measures.

The most reasonable analysis here at a minimum has to include as a bad thing deaths, transplantations and discontinuation for worsening disease. When you've just made those adjustments, you're already way from that .01.

Close? Okay. Maybe you could say so, but you haven't begun to adjust for what are certainly last observation carried forward, which I cringe when I see this, particularly in a setting where it truly is challengeable.

But we have the two fundamental assumptions hold here. One is uninformative missingness, and the second is lack of changes over time. Both of those don't hold.

And so to say that we are statistically

close is very controversial here. If you had a reliable primary analysis on quality data and you needed an .01 and you got an .013, sure, you're close if that helps you. If you get an .05, you're not close to .01.

DR. LIPICKY: So then, in fact, you wouldn't want to pursue the rest of these questions because you don't think it's close.

DR. FLEMING: I'm arguing we should always pursue issues that look at the totality of data. We should focus, first and foremost, on the primary endpoint. My major challenge was to make the assumption that we are close on the primary endpoint, let's go from there.

I'm saying that's controversial.

DR. LIPICKY: Okay.

DR. FLEMING: It's certainly, I think, not close, not controversial to say we're not close based on the estimate from what we were targeting. We're not close, and from a statistical significance, I'm saying it's controversial to make the assumption of the statement that we're close.

DR. LIPICKY: But then I was told if you don't think you're close on the primary endpoint, you shouldn't look any further. Do you disagree?

DR. FLEMING: Well, I don't agree with that.

DR. LIPICKY: You don't agree with that.

DR. FLEMING: I do think we need to look at global benefit to risk, although I would -- what I do agree with with that statement --

DR. LIPICKY: Okay. No, no, no. Fine.

DR. FLEMING: -- it takes a far more compelling result on supported measures --

DR. TEMPLE: Tom.

DR. FLEMING: -- in a highly safe intervention.

DR TEMPLE: Let me say what the premise for that was. You might not agree with it.

If you just totally lose, show nothing on your primary endpoint, it's always been considered sort of disreputable to go nosing around. On the other hand, if you are close on your primary endpoint, you have somewhat greater credibility when you go

nosing around for support, which is why the question is framed that way.

So the discussion you've just had is important. By p values you might say it's close, but you suspect that those p values are overstated for the reasons that you gave.

The other thing you've said though is something of a puzzle to me. People's guess as to what the effect size is going to be is nothing more than a guess. I've never heard quite so strong a statement that failing to be as good as you hope to be is a real disaster, and that troubles me.

I think those are largely made up and designed to, you know -- people figure the sample size in reverse and then go back and calculate it. I give those things no credibility at all.

Now, if someone were to say, "I don't think an effect size of more than X would be worthwhile," that's a different question, but I don't believe that's what they said.

DR. FLEMING: And I agree with you. I would not say failing to achieve the targeted effect

is a disaster. I would not use those terms. What I would say is the targeted effect ought to have been carefully laid out and ideally ought to be a representation of the smallest difference of clinical relevance. If a much smaller difference would have been clinically relevant, then we should have seriously considered targeting such an effect.

But this is not a matter of 55 targeted, we achieve 40 because I would be with you all the way in that case.

DR. TEMPLE: In this case they've said something different, and of course, it's after the fact. So we don't know. They've said expecting a big increase in exercise was a mistake in this population. What we really should have looked for was a modest, if any, improvement in exercise and more comfort in reaching it.

Now, of course, that's plausible, but after the fact.

DR. FLEMING: Exactly.

DR. TEMPLE: The thought of this question was, okay, you're allowed to think that way a little

bit if you're pretty close on your primary endpoint, and you really mustn't do that if you're not pretty close. That was the thought.

DR. FLEMING: And that's right. If one draws the conclusion that you're close, I fully support your logic.

DR. LIPICKY: But did I misunderstand, Tom? You said you're not close on the primary endpoint.

DR. TEMPLE: Because he believes there was informative censoring and that those p values are overstated.

DR. LIPICKY: Well, no. The loose, generous rules that were drawn up were an order of magnitude off, and then the point estimates and the p values calculated miss the determined one that was generous, and then if you make any kind of adjustment to it, it gets worse.

So what Tom is saying is this is not a close call from that point of view. It's just flat out losing.

DR. TEMPLE: Right. That's what Tom says

because of the feeling that was censoring.

DR. LIPICKY: I just want to make sure Tom didn't --

DR. FLEMING: If you'll allow me, I know the discussion is dragging on. Let me be ten seconds concise as summarizing what I am saying. I believe we are not close in the clinical achieved effect relative to what was targeted, relative to what Flolan would deliver.

We didn't have to achieve that full effect, but I say we weren't close in the clinical effect, and I'm also saying it's controversial to state that we're close statistically. I think reasonable analyses that are done would show that we clearly didn't hit the target, and in fact, could reasonably show we weren't close to the target, but some of those are controversial.

So it is controversial at best to say that you're close on the statistical analysis.

DR. TEMPLE: Okay, but that second is the question that's at issue here. I mean whether you value the effect size is an entirely different

question.

CHAIRMAN BORER: Are we going to get to that one or do you want some discussion here about that since we're advising you?

DR. TEMPLE: Jeffrey, can I say what I understand?

CHAIRMAN BORER: Yes.

DR. TEMPLE: I think Tom says that the nominal p values are overstatements. Therefore, the nominal p values, which are fairly close to the target don't represent reality and should not be taken at face value. Therefore, it's not particularly close.

CHAIRMAN BORER: Okay.

DR. TEMPLE: I'm not certain I can tell that everyone agrees with that, but I think that's what Tom was saying. Right, Tom?

DR. FLEMING: Fair enough.

CHAIRMAN BORER: Okay. I think so you can have my opinion on record here that there are a number of ways to look at these data, and Tom outlined them all, and the FDA made some suggestions about

adjustments. I really have no idea which adjustments are appropriate or inappropriate, and I think that Tom's comment about the controversial nature of the assumptions about statistical significance is the correct one.

I think that the range of responses to statistical analysis go from pretty close to what the prespecified rule was to not at all close to what the prespecified rule was, and again, I'm not sure what's right, and I would tend to look for overall consistency of the data to determine whether I'm willing to accept the consistency of the primary endpoint or not.

But whether you want to hear it at this point or not, I'm going to say something about the magnitude of effect. I think that it is very, very difficult to determine the clinical importance or the clinical value of the drug in making people feel better when the measures that we use are highly variable, don't deal directly with the issue that we want to get our arms around, which is very difficult to do in any event. Whenever you deal with

symptomatic endpoints there's controversy about how you measure them.

And the fact that the effect size on six minute walk was smaller than expected or looks modest or whatever, I'm just not sure that that's very important. I would like to see that there's consistency among all measures of symptomatic benefit, and whether I think there is or there isn't we'll get to in a while, but I really don't think that we ought to focus on the magnitude of the change in six minute walk.

It just is one of many ways of looking at a problem that we're trying to deal with here. We've heard data about the other ways of looking. If we want to say, well, the statistical significance of the result, that is, the consistency of the result across the studies, which is what we're talking about, is inadequate to allow us to make any judgment, therefore, there's no point in looking at other endpoints, well, that may be reasonable. I'm not sure anybody has said that.

I think Tom's point was, well, we're not

sure. It's controversial. You could say it's significant. That's close. You could say it's not.

But if it's relatively consistent, everything went in the right direction, then I think it is reasonable to look at other endpoints than the six minute walk. In fact, I think it's absolutely imperative to do that. I think we would have demanded it if the sponsor didn't do it, and I think that, therefore, the magnitude of the effect has to be judged as a global entity, not just on the basis of a six minute walk test that's a highly imperfect way to summarize symptom status.

Now, again, later we'll get to the point whether the data as a totality do convince us or not, but I think that point ought to be made.

Steve, Dr. Brem, Michael Artman, do you have anything else?

DR. NISSEN: I do. I think it's fine to hold a sponsor's feet to the fire on the primary endpoint when you're talking about a drug that you're going to potentially expose very large numbers of people to, where your confidence of it just has to be

at a certain level.

When you talk about an orphan disease, I think you have to look at it differently, and I think that this is such a disease. I think it's also important for us to realize that in interpreting these data, the people who use these drugs are the "cognizanti" (phonetic). These are a specialized group of physicians that are very skilled at assessing these patients and will bring to the table skills that are very high in interpreting who might get the intravenous therapy, who might get the subcutaneous therapy or any other therapies that come along.

And so I'm willing to look at these secondary measures more liberally in a situation where the ultimate exposure risks here are very different than I think they might be for a drug that's going to be used by family practitioners in a large number of people.

And so it does influence me, but not for every case, but for this case. I am influenced by the totality of the data as much as I am by that primary endpoint.

DR. TEMPLE: Do you agree though that you have to believe the primary -- I mean, one of our premises was that you need to believe the primary endpoint is at least pretty close. Otherwise you're noodling.

DR. NISSEN: Yeah, and I agree with that, Bob. I think that the primary endpoint ought to be fairly close. Now, I don't know. I mean, the case has been made that it's not close. I don't think that's right. I think that they got pretty close on the primary endpoint, and with these other efficacy measures, I am willing to look at the totality of the data because I think they were close on the primary endpoint and because the mitigating circumstances of the disease that's being treated has to let us think a little bit more with our hearts on this one than with our heads.

DR. FLEMING: But, Steve, would you grant that what you're saying about this being an uncommon setting we're setting, that the accommodation that you have argued for has already been granted, i.e., we weren't asking for the standard for strength of

evidence, .025 squared. We were allowing a tenfold order of magnitude, an order of magnitude less stringent criterion, and that wasn't hit.

So what you're saying has, I think, already been acknowledged in the revised, much weaker standard that was agreed to when this study was designed.

DR. NISSEN: I understand your point. I guess I just don't agree with you.

DR. HIRSCH: Steve Hirsch on this one more time.

What is the compelling case here for changing what is usually your standard?

DR. NISSEN: Because this is a disease for which there is very limited treatment. It's an orphan disease. It's a disease where the existing therapy has major disadvantages and where I believe that the people that will be able to use this therapy are very limited and very likely to be highly expert in administering such therapies.

I think we can be more liberal in an orphan disease setting than we can in a drug for

hypertension, let's say.

DR. HIRSCH: But do not we then, therefore, want for this population to know for sure truly whether there is benefit because, in fact, it is a desperate situation?

DR. NISSEN: Well, again --

DR. HIRSCH: We have to face that together.

DR. NISSEN: Again, I agree with that, but I think they were very close on their primary endpoint and looking at the totality of data, I believe that there was benefit.

CHAIRMAN BORER: Michael, do you have anything? No.

Dr. Anderson, any comment? No.

Okay. The next section of this question, let's skip 1.1.2. I think we've sort of done that. No, we haven't?

DR. LIPICKY: Yes and no, right? Because now you're going to look at the totality of data

CHAIRMAN BORER: Okay. Specify --

DR. LIPICKY: So 1.5.2 says before you

look, tell us what you're going to look for. You've already seen it, right? So you already have some intuition about what leads you what direction or another, but this 1.5.2 says make up some rules right now for how you're going to do that and how this totality of data is going to be assimilated so that you'll be able to say something at the end.

Do you want to try to take that on?

CHAIRMAN BORER: Sure.

DR. LIPICKY: Okay.

(Laughter.)

CHAIRMAN BORER: I'll tell you I think that if we have just the data set that's available to us, that's been presented to us, there have been analyses of all the endpoints that were measured, all of the measures that were used have been presented to us. I think that if we look at all of them just as we do when we study drugs for heart failure and determine that they are consistent, that is, they all go in the same direction or at least that there isn't something that goes very much in the opposite direction from the sense of all the other data, that we can come to a

conclusion about the consistency of the data and the reasonableness of use of the drug.

Now, the strength of the data is a different issue, and I certainly agree with what Alan is suggesting. At the end of the day we don't want to approve a drug for a relatively small group of very sick people because we hope it works. We have to have some reason to believe that it works, and that the benefit associated with its use outweighs the risks associated with its use.

But having said that, I think that we've seen a group of measures all of which are reasonable, and we can look at them and determine whether they all go in the same direction. If five out of five do, that's part of people's .03.

DR. LIPICKY: You need to say a few more words. There are 16 of them there. They're all bullets. So are you going to look at p values for mortality? Because, you know, you've got to correct -- you've got to divide the p value by 16, or do you just want to look at point estimates or you want to look at confidence limits or how are you going

to handle this?

CHAIRMAN BORER: I'll look at point estimates, and I'll look at p values.

DR. LIPICKY: Okay.

CHAIRMAN BORER: For each one individually.

DR. LIPICKY: Okay.

CHAIRMAN BORER: On an exploratory basis, and what I said was that none of these should go in the wrong direction, and so far as I can tell, none of them did. We didn't see a benefit in terms of mortality and hospitalization, but we didn't see a detriment, et cetera, et cetera.

DR. LIPICKY: Well, the confidence limits are wide. So you won't have very much --

CHAIRMAN BORER: That's true.

DR. LIPICKY: -- confidence in the thing, but that's all right. Do you have these numbers anywhere that you could easily say what the relative risk for mortality is?

CHAIRMAN BORER: I can't quote it to you. We saw the numbers.

DR. LIPICKY: I was asking the sponsor if they had some -- for each of these bullets under 1.5.3, you have all of the numbers. Could you just say them?

DR. TEMPLE: Jeff, presumably you were going to look at the things that were potentially evaluatable by the study, that is, the very symptom things which had enough numbers to possibly have an effect and see if they did. You probably can't make too much out of something where the numbers couldn't possibly have led. Well, not possibly is wrong, but were unlikely to have led to anything. So you are going to make that distinction.

CHAIRMAN BORER: I would, indeed, but I think that the discussion is being confounded by an effort to look for an effect on natural history when, indeed, that wasn't the aim of the development program, and Ray told us earlier that it wasn't because the FDA didn't ask for that.

It doesn't seem intrinsically unreasonable to me not to expect a benefit in terms of natural history if, in fact, you improve quality of life and

reduce symptoms for people with a disease and don't diminish the length of life sufficiently so that someone who knows it's going to be diminished would not accept the therapy because of that diminution.

And we haven't heard anything to suggest a detriment of any kind, much less a major detriment on the natural history of the disease. It seems from the relatively small number of data that we have here that there doesn't seem to be much effect, although we heard about a reduction in certain measures of progression that may be softer than mortality in hospitalizations.

DR. TEMPLE: It's on the screen behind you.

CHAIRMAN BORER: I'm sorry?

DR. TEMPLE: It's on the screen behind you.

CHAIRMAN BORER: Yeah, okay. Well, you know, we have that, but at least the point is that it doesn't look like this agent is killing people while it's trying to make them feel better, and I think that that's what we need to know. That was the aim of the

development program.

We shouldn't ask of the development program something that wasn't required of it.

DR. HIRSCH: Agreed. Disease modification is the Holy Grail of what we want to all accomplish, but that was neither the design question, nor was there data presented to help us with that.

So let's come back to Ray's question, which is when we want to look at the totality of the data and the multiplicity of positive signals, how do we take a multiplicity of signals, which I think are generally positive, and come up with an analysis, a ranking, an integrated plan to say that we now believe that beyond gestalt there's benefit? Because gestalt is a very hard way to approve a drug.

And I think there was a history to this which we've always leaned on, just to say it again out loud, which is you can create any combination of outcome variables you want, but you pre-define them, and you design a trial to achieve that with statistical significance.

So I think it's very hard, Ray, to ask us

at this point to come up with a post hoc algorithm.

DR. KOCH: The analysis plan did specify how the secondaries were going to be looked at, and the principal reinforcings were looked at first. That was the composite score for signs and symptoms.

CHAIRMAN BORER: Excuse me. Dr. Koch, can I ask you please to sit down. Let us go through our deliberation here.

DR. HIRSCH: But I'll take Gary's point, which is exactly that. He did present a plan that was pre-defined and that's all we have. Beyond that I think it becomes guess work.

CHAIRMAN BORER: Okay. Do formal retrospective analyses of combinations of the selected primary and secondary endpoints further support the effectiveness of treprostinil?

I think we've been talking about that, and if so, did such an analysis give appropriate weight to its components?

Do you really want us to answer that, Ray?

DR. LIPICKY: No, that's okay.

CHAIRMAN BORER: Okay. How many such

analyses were there or were possible? Again, we can do that off line.

Considering all pertinent data, is treprostinil and effective treatment for primary pulmonary hypertension? That's effective, not is it acceptably safe for its intended use as well as being effective.

Let's just hear a yes or a no starting from the left-hand side, Alan.

DR. HIRSCH: I don't know why you always do this to me. Probably, but I am not sure.

CHAIRMAN BORER: Okay. That's good enough.

(Laughter.)

CHAIRMAN BORER: Paul.

DR. ARMSTRONG: Maybe, but not on what I've seen.

CHAIRMAN BORER: Okay.

DR. LINDENFELD: I'm not sure either, but I think the answer is probably yes.

CHAIRMAN BORER: Tom?

DR. FLEMING: (Pause.) Well, if the

question is specifically efficacy alone, my sense is that we have not established the benefit on the primary endpoint. I believe that it is important in any study to look globally at all relevant supported information.

I believe very much in the spirit of what Bob Temple mentioned before as to the manner in which you interpret that, i.e., if you're not at all close to hitting the primary endpoint on efficacy, then it takes very much more in supportive measures in order to swing the conclusion in the other direction, and that interpretation I would believe is influenced by the clinical importance.

So if we were looking at improvements in mortality, improvements in hospitalization and improvements in clinical deterioration, those would be especially persuasive to me. Those showed no difference.

What did show a difference were relevant, clinically relevant, supportive measures, and there were a wide array of these. They were not all uniform in the nature of the effect that they showed. The

effect was fairly modest.

So from an efficacy perspective, we didn't hit what was the targeted measure. We also showed no evidence of benefit on what are even more clinically important measures.

We did see an indication of a modest benefit on some of the secondary measures that relate to symptoms.

CHAIRMAN BORER: Michael.

DR. LIPICKY: Is that no, Tom?

DR. FLEMING: It is what I said it was, Ray. Answers are not always yes or no, right? Because, in essence, the answer for what the efficacy effect is then has to be put in the context of safety, and it's --

DR. LIPICKY: Maybe.

CHAIRMAN BORER: Mike, Michael, yes or no, or all answers are not yes or no.

DR. ARTMAN: Probably.

CHAIRMAN BORER: Dr. Anderson.

DR. LIPICKY: Maybe is all right.

DR. ANDERSON: It seems to be, based on

the data that I've read, it seems to be a treatment. I question the word "effective," and that's, again, based on the data.

But, Mr. Chair, I would like to agree with what you said earlier about how we ought to go about this thing.

CHAIRMAN BORER: Okay.

DR. TEMPLE: We need to be sure what we're asking. I mean, in the end, this committee, to give us a meaningful recommendation,has to be able to say without breaking into a smile that there is substantial evidence of effectiveness from adequate and well controlled studies.

I don't think anybody has raised questions about whether the studies were well designed, and we acknowledge in a variety of places that substantial evidence has kernels of judgment in it, but probably and things like that have to be translated into do I believe -- is my conclusion as an expert that this is convincing enough for me to say that?

So we need to know that answer eventually.

CHAIRMAN BORER: Steve?

DR. NISSEN: Do I believe that the evidence supports efficacy? And the answer is yes.

CHAIRMAN BORER: Okay. Dr. Brem.

DR. BREM: I believe it probably does show efficacy.

CHAIRMAN BORER: I'd like to see more data, but if I had to pick an answer now, I'd say yes.

DR. FLEMING: But with your clarification, Bob, as to whether these data establish substantial evidence of efficacy in the spirit of what we would appropriately anticipate in this setting, taking into account what it was that these studies were designed to address, no, it does not.

CHAIRMAN BORER: Over what period of administration of the benefits of treprostinil manifest --

DR. LIPICKY: If you'll forgive me, I hate to draw this out, but I recorded five maybes, and if you want to listen to Bob Temple, those maybes have to be turned into yes or nos.

CHAIRMAN BORER: Sorry. Okay. Let's turn them into a yes or a no. Starting on the left, Alan?

DR. HIRSCH: I'll say no.

DR. ARMSTRONG: No.

DR. LINDENFELD: Yes.

DR. FLEMING: No.

CHAIRMAN BORER: Okay. The others were neither maybe?

DR. ARTMAN: Yes.

DR. TEMPLE: They were yeses.

CHAIRMAN BORER: Okay. Alan Hirsch voted no. Paul voted no. Yes, JoAnn voted yes. Tom voted no. I voted yes. Steve voted yes., and Dr. Brem voted yes. Dr. Artman -- Michael, was that a yes or no?

DR. ARTMAN: Yes, that was a yes.

CHAIRMAN BORER: That was a yes, and, Dr. Anderson?

DR. ANDERSON: Yes.

CHAIRMAN BORER: Yes. Okay. So six yes and three no for is it effective. We haven't discussed magnitude, et cetera, et cetera. Just is it an effective treatment.

Over what period of administration are the

benefits of treprostinil manifest?

I think that I'll take the -- to cut down the duration of our discussion, note that the studies went on over three months. We really can't talk about any period beyond that.

Would anybody disagree with that? No.

Over what dose range are the benefits of treprostinil manifest?

Again, we can only talk about what we were shown. There was no formal parallel design dose response study performed. We only know that benefits were seen within the range that was described in the materials from the study. We can't go beyond that.

Two, the dose of treprostinil rose steadily during treatment. Was this because of forced titration?

Tom, is there any -- we discussed all of these. Is there any additional point you'd like to make as the committee reviewer about this? We talked about these possibilities.

No, okay. Ray do you have enough comments from us over the course of the morning?

DR. LIPICKY: Yes, it's more than enough.

CHAIRMAN BORER: Okay.

DR. LIPICKY: I guess what it says to me is that one doesn't know quite what dose to give. One just knows what doses were given.

CHAIRMAN BORER: That's right.

DR. LIPICKY: And so the question is -- the next question, the 2.2, is that an approval issue? So you have an effective drug, and you don't know how to give. What do you say for instructions for use?

CHAIRMAN BORER: Yeah, the issue of writing a label is a very important one, and that's what we get to here at 2.3. Would anybody like to make any comments about how the label should describe dosing?

DR. LIPICKY: It's okay if you don't. You don't have to if you don't feel that you can.

DR. TEMPLE: Wouldn't you do it the way they did it? I think the question is whether you can go higher as they did in the extension, which doesn't have any controlled data.

CHAIRMAN BORER: Yeah, we don't know. We

don't know. I mean, I think we can only say that if we say the drug is effective, it was effective as it was used, and it was used in the way that was described in the material we got from the studies.

Infusion site pain was a problem often requiring management with opioids, 3.1 Are the long term data reassuring about infusion site pain? Is that the --

DR. LIPICKY: That pain goes away.

CHAIRMAN BORER: Okay. Does anyone have a comment about that, anyone on the committee?

I will suggest for the committee that the long term data are suggestive that the problem isn't the major one. I don't know whether the pain goes away. I don't think we can really talk about that.

DR. HIRSCH: What you can say is that it didn't limit drug usage.

CHAIRMAN BORER: I'm sorry? What did you say, Alan?

DR. HIRSCH: Whether it goes away or not, it didn't limit protocol use of the drug.

CHAIRMAN BORER: Okay. Which is 3.2. Is

the pain --

DR. FLEMING: Just one other quick comment on 3.1. It's very relevant and certainly of great interest to know what both efficacy and safety would be over a longer term, and the 06 data is there to provide some level of insight, but those data are also -- need to be interpreted with considerable caution.

We saw, for example, that use of opioids, I think, reduced from 27 percent in 04-05 to 21 percent in 06. What I don't know is of those people that were in 06, they weren't all of the 0405 people, and maybe the particular people with more serious problems with pain never got into 06, and so I can't tell whether this 21 percent is truly a reduction. It may actually be an increase from the subgroup in 06 who had actually be in 04-05.

So I would argue that it's reassuring in the sense that we're not seeing tremendous increases. We're not seeing evidence of significant deaths occurring, again, though I would hope that the intention is to see an improvement in overall survival. The data have to be interpreted with great

caution in terms of efficacy and safety.

CHAIRMAN BORER: Okay. I think we'd all agree with that. All the same, we didn't hear about a problem. That doesn't mean there couldn't be one or might not be one, but we didn't hear about one.

If treprostinil were approved, how should the label describe this? Do we have any specific comments?

DR. LIPICKY: No, I think you told us.

CHAIRMAN BORER: Okay.

DR. LIPICKY: We're fine on that.

CHAIRMAN BORER: Okay.

DR. LIPICKY: You can skip four if you would like.

CHAIRMAN BORER: Okay. Then let's go to number five, which is the issue of the efficacy versus the safety for the intended use. I'm going to -- may I add a rider to this one, Ray, number five?

Specifically, if we suggest that the drug is approvable, is there additional information that should be mandated to be obtained? Is that reasonable? And if so, what?

DR. LIPICKY: Well, I guess you can suggest that.

CHAIRMAN BORER: Okay. Thank you.

DR. LIPICKY: I mean, how could I stop you?

(Laughter.)

CHAIRMAN BORER: Okay. For a change we'll start at the other end of the table here. This is the key question, number five. Michael Artman.

DR. ARTMAN: Yes.

CHAIRMAN BORER: Okay. Dr. Anderson.

DR. ANDERSON: Yes.

DR. NISSEN: Yes.

CHAIRMAN BORER: Okay. That's three yeses.

And if you have any additional opinions about why your answer is what it is beyond what you've already said, this is the time to say it.

DR. BREM: Yes.

CHAIRMAN BORER: Okay. I'll vote yes, but I do believe that there are additional data that should be mandated if the drug is approved. It should

be mandated to be obtained in Phase IV specifically with regard to duration of effect, perhaps with randomized withdrawal studies or what have you since we're told that there is no evidence of rebound, although we ought to know that.

And I think we need considerable additional data about dosing, which could be obtained in Phase IV.

Tom?

DR. FLEMING: The study showed in what it was designed and targeted to show much more modest effects on the primary endpoint than had been intended, effect that, in fact, are very controversial as to whether they're reliably established. In fact, I believe they are not.

The secondary measures that are also very critical as predefined as principal reinforcing endpoints on major sequelae consistently show not only non-significant effects, but no positive trends.

The supportive measures that are symptoms show clinically modest effects. These effects though are not achieved without some very significant and

frequently occurring major issues that relate to pain, with a substantial increase in the use of opiates and anti-inflammatory drugs.

I strongly argue it should not be approved.

CHAIRMAN BORER: Okay. JoAnn?

DR. LINDENFELD: I would vote for approval. I think overall I think that there's a lot of signals that this drug is effective in a difficult population. We have another drug similar to it that is effective, and I do think though we need some additional data, particularly about withdrawal of this drug and whether or not there are hemodynamic or clinical changes following withdrawal.

CHAIRMAN BORER: Paul?

DR. ARMSTRONG: I don't believe this meets the standard of evidence that we have applied to other therapies, sometimes in common diseases, or the standard of therapy currently available for this treatment, and although there are some promising signals, it does not for me reach a level of confidence for approval. So no.

CHAIRMAN BORER: Alan.

DR. HIRSCH: I'm sitting here taking notes.

You've heard me comment as we've gone through this. I really concur that we ideally as a committee would want additional data to push us over the edge for unambiguous, clear cut gestalt and statistical efficacy.

And actually I don't think a signal, which I think is clearly there without any question as a gestalt cardiologist, is enough to bring us all the way to approval, and I mean this as someone who has advocated for orphan disease care.

I think in particular diseases that are so severe, so potentially mortal, and so hard on the soul require flexibility and proof, and with that you know where I'm leading.

Not a slave to p values, I would say yes, but I think that we need more evidence, and I'm going to give my final answer as no, with regrets.

CHAIRMAN BORER: Okay. What you've heard then, Ray, is a committee that's sort of on the edge,

teetering towards approval rather than teetering against in the majority view, but if the agency does choose to approve the drug, there clearly need to be additional data obtained so that a reasonable label can be written or the label can be approved upon.

DR. LIPICKY: Otherwise people with an orphan disease will be fooled into taking something that probably doesn't work. Is that it?

CHAIRMAN BORER: No, no, no. I wouldn't have voted yes if I thought they were going to be fooled into taking a drug --

DR. LIPICKY: I see.

CHAIRMAN BORER: -- that doesn't work.

DR. LIPICKY: Okay. So you don't --

CHAIRMAN BORER: My issues were with regard to duration --

DR. LIPICKY: It's not so wishy-washy then. The yeses are really yeses.

CHAIRMAN BORER: Oh, yes. The yeses are yeses. The yeses are yeses.

DR. LIPICKY: Okay.

CHAIRMAN BORER: Although there are

additional data that we believe would be required to provide --

DR. LIPICKY: In order to --

CHAIRMAN BORER: -- optimal information --

DR. LIPICKY: -- that it be approved.

CHAIRMAN BORER: -- for use, and it's the absence of those data --

DR. LIPICKY: So you want to --

CHAIRMAN BORER: -- that need to teeter.

DR. LIPICKY: -- clarify the use of the drug.

CHAIRMAN BORER: Yes.

DR. LIPICKY: You think it works. You need some post marketing studies that will help amplify the directions for use.

CHAIRMAN BORER: That's right.

DR. LIPICKY: And so it isn't a question of does it work or not. You're comfortable with that.

CHAIRMAN BORER: I'm comfortable with that.

DR. LIPICKY: But you need more information with respect to how it should be used.

CHAIRMAN BORER: right.

DR. LIPICKY: Okay. Fine.

CHAIRMAN BORER: Are there any other comments by anybody on the committee?

(No response.)

CHAIRMAN BORER: If not, I think we've given you our best advice.

DR. LIPICKY: Fine. When should we come back?

(Applause.)

DR. LIPICKY: When should we come back?

CHAIRMAN BORER: Oh, I'm sorry. Yeah, there's a lunch break here it says, and we'll start again at two o'clock.

(Whereupon, at 1:14 p.m., the Advisory Committee meeting was recessed for lunch, to reconvene at 2:00 p.m., the same day.)

AFTERNOON SESSION

(2:07 p.m.)

CHAIRMAN BORER: The committee will provide advice regarding NDA 21-321, Extraneal, peritoneal dialysis solution for treatment of chronic renal failure.

Before we begin the presentations, I mentioned this morning that there was an additional request for a public comment from Dante Germanotta and Joan Standaert will read the submission that was sent.

MS. STANDAERT: This is a written statement from Dr. Dante Germanotte. He is a dialysis patient on peritoneal dialysis.

"It is urgent for me that the peritoneal dialysis solution, Extraneal, 7.5 percent isodextrin, become available for PD patients in the United States as soon as possible. My hope is that this hearing will recommend approval of Extraneal and be put in a priority category.

"Extraneal was the subject of a number of presentations recently at the American Society of Nephrology in Miami. In these presentations, it was

pointed out that significant cost savings can be achieved during the period of extended treatment life achieved by delaying the transition of patients to hemodialysis through the use of Extraneal.

"Also, Extraneal provides greater peritoneal dialysis technique survival and biocompatibility when compared to the glucose based peritoneal dialysis.

"I am getting less and less fluid out of my body after using the glucose based solution for four years and will have to shift to hemodialysis much sooner than I had hoped. Extraneal will extend my life on PD which has provided me with an unusual amount of mobility and flexibility in my life's activity.

"When I heard about Extraneal and that it had been used by patients in Europe and Canada for some years now, I thought about moving to another country to get access to Extraneal. It is that important to the quality of my life. I can't tell you how pleased I am to know that it may become available to patients in this country.

"This hearing is a significant step in this process, and as a retired college professor who is a young 71, and my wife Betsy and I have much still to accomplish before my energy gets drained by hemodialysis."

Signed, Dr. Dante Germanotta, Professor of Sociology, Emeritus.

CHAIRMAN BORER: Thank you.

Now we'll move on to the formal presentation, which because of the delay in beginning the session we'll allow with the discussion to run until just about 3:15, and again, as this morning, I'll ask the committee to hold questions until after each formal presentation so that we can make it through this session reasonably efficiently.

Dr. Mujais.

DR. MUJAIS: Mr. Chairman, ladies and gentlemen, good afternoon.

Thank you for the opportunity to come before you and discuss our new solution for peritoneal dialysis, Extraneal.

We have before you today two groups of

individuals. The first represent Baxter participants that consist of our medical, statistical, science and development, and regulatory people.

We also have a group of consultants that we have asked to be present to help us address some of the questions. Many of them are leading experts in their areas, particularly in nephrology, cardiology, dermatology, biostatistics, and quality of life issues.

Extraneal, a new dialysis solution, was first marketed in Europe in 1992 by ML Laboratories, and it has been in use, clinical use, in the U.K. since 1992.

It was licensed by our company in 1996, and since that licensing, we've had marketing approval in 31 countries that include all of Europe, many countries in the Middle East and Asia and Latin America and Canada.

Currently we have around 8,200 patients that are being treated with Extraneal as of today, and the proportion of patients in Europe that are utilizing this solution consist of 30 percent of all

PD patients in Europe.

The U.S. clinical trials began in 1997 with consultations with the division, and we were granted orphan drug designation in 1997. This granting of orphan drug is based on the fact that the population that receives peritoneal dialysis in the United States consists of under or just around ten percent of patients on dialysis, and numerically that amounts to only 25,000 patients in the United States that receive peritoneal dialysis.

Our NDA was submitted in December of 2000.

The indication that we are proposing is as follows. Extraneal is indicated for a single daily exchange for the long dwell, eight to 16 hours, during continuous ambulatory peritoneal dialysis or automated peritoneal dialysis for the management of chronic renal failure.

The topics that have been identified of interest by the division and offered to your committee cover areas of the efficacy of our solution, the aspects of quality of life, our database and the safety profile, and we will attempt during our

presentation to cover these issues as well.

In order to be able to present our data and our answers to the questions in an organized fashion, we propose that first we discuss with you the clinical and physiologic rationale for development of this new solution.

We will follow this by a discussion of our clinical trial experience.

And finally, we will conclude and address the questions.

Icodextrin, the osmotic entity within our solution Extraneal, is a polymer of glucose, and it consists of long chains of glucose molecules that are linked between Carbon-1 and Carbon-4 for the main chain, and this one-four linkage constitutes 90 percent of the linkage within the polymer.

There is also a one-six, Carbon-1 to Carbon-6, linkage in some of the branches of the polymer, and this constitutes under ten percent of the branching and linkage within the molecule.

Because of its origin from corn starch and the fact that it consists of polymers of glucose,

there are enzymatic systems within the body that are capable of breaking down these polymers down to glucose. So the final end product will be glucose after metabolism in the body.

The solution in which Icodextrin is used is identical in its electrolyte constitution to the current Dioneal (phonetic) solution, PD-2, that is on the U.S. market. The difference consists only in the nature of the osmotic agent that is used to effect ultra filtration after peritoneal installation. While Dioneal has 1.5, 2.5, and 4.25 percent concentrations of dextrose, Extraneal has 7.5 concentration of Icodextrin.

Also, because of the differential in the size of these molecules, the osmolarity of the solutions will be different, and with Dioneal we have osmolarities that range between 346 to 485, whereas with Extraneal the osmolarity of the solution is identical to normal plasma, between 282 to 285.

But for all other constituents of the dialysis solution, Extraneal and Dioneal are identical.

The rationale for development of this solution we will discuss by covering three areas. The first is the area of an unmet clinical need in this dialysis population. We'll follow that by a discussion of the limitations of the current osmotic agents, in particular dextrose, which is the only osmotic agent available in the United States.

And finally, how the kinetics of Extraneal can match the clinical requirements and why the product was developed for that purpose.

Patients on peritoneal dialysis in the United States continue to have significant problems in their fluid management, and next to hospitalizations because of vascular access, hospitalizations because of fluid overload are the leading cause for hospitalization within the HCFA database and the U.S. RDS database in the United States.

Now, symptomatic fluid retention occurs in 25 percent of all PD patients, and this is fluid retention that can manifest as lower extremity edema in a large number of these 25 percent, but additionally there could be also pleural effusions and

pulmonary congestion.

This high proportion of symptomatic fluid retention is not unique to patients in the United States, but has also been observed in other countries during utilization of glucose based solutions, and similar proportions are available from publications from Japan, the Netherlands, and Sweden during the early and mid-'90s.

The reasons for these limitations have to be thought for in the approach of nephrologists for management of fluid balance in patients on dialysis. Naturally, as nephrologists, we advise our patients to adhere to dietary restrictions. However, dietary counseling in dialysis patients has elements of complexity to it. We are not advising them only to restrict solute and water, but we also advised them to restrict phosphate intake, potassium intake, and the nature of protein intake that they go under.

The patients also are delivering the therapy to themselves. So the element of compliance is layered. It's not only dietary compliance, but also compliance with the therapy, and they have an

extensive pharmacopeia that they need to take. On average, a dialysis patient can take between seven to ten drugs a day.

So the complexity of compliance is an issue that may lead to limitations in fluid management.

The second aspect that may contribute to this is renal excretion. These patients, when they present to dialysis, already have very advanced renal failure, and their residual renal function is such that their urine output is quite decreased, and ultimately while on therapy, they will progress to total anuria.

And even when they have some urine output, they have a significant degree of diuretic resistance, and they will require very large doses of loop diuretics (phonetic) and in addition to metolazone (phonetic).

So their response to diuretics is at best limited, and when they become totally anuric, they become totally dependent on peritoneal ultra filtration.

Now, the primary focus of dialytic therapy in these patients is to control fluid management, fluid volume in them, and to remove toxins. So with the dietary limitations and the constrained renal excretion, their dependence on peritoneal ultra filtration is almost total for fluid management.

Currently we have two forms of delivering peritoneal dialysis in the United States and worldwide. The first form relies on an automated system where patients during the nighttime receive several dwells of dialysis solutions, and during the day, they have one dwell usually that resides in the abdomen for the entire duration of the day.

Now, this is the time period during which we are proposing that Extraneal we used. Its usefulness is during this long dwell.

Currently 60 to 65 percent of adult patients in the United States are using the automated variety of peritoneal dialysis. This proportion may even be higher among children for obvious reasons of flexibility and quality of life and ability to deliver the therapy.

And the other proportion of patients on peritoneal dialysis, the chronic ambulatory peritoneal dialysis, the short dwells are delivered during the day in a manual process that the patient performs on their own, but during the nighttime while the patient is sleeping, there is a long dwell of peritoneal solution in the patient's abdomen.

In CAPD, the average duration of the long dwell is between seven to 12 hours. In APD because this is a daytime and evening long dwell, the duration of the long dwell can extend as long as 16 hours.

The reason for the long dwell in patients in peritoneal dialysis is basically because of the imperative of removing toxins. Treatment during the nighttime in APD patients, particularly in adult APD patients, may not be sufficient to reach the solute removal levels that have been recommended by the medical guideline authorities.

So small solute removal, while flow dependent and can be enhanced during the nighttime in APD or daytime short exchanges during CAPD, still requires additional solute and toxin removal during

the long dwell.

But as important, middle and large molecular weight toxin removal is time dependent. So accelerating or increasing the flow component of the therapy does not enhance the removal of middle and large molecular weight toxins. An example of these toxins would be Beta 2 microglobulin, which deposits in the joints of patients and in other major organs, including the heart and can cause morbidity in this population.

So a continuously wet abdomen is required for the success of the therapy in adult patients.

The other aspect related to the reason why we have a long dwell is that this is a therapy that is performed by the patients themselves at home, and realistically for the therapy to remain logistically feasible, we need to have also these periods of long dwell. We cannot have short dwells continuously in the 24 hour period.

Now, dextrose is the current osmotic agent that is used in dialysis solutions in the United States to effect volume removal. An examination of

the kinetics of dextrose will help us understand the limitations of this agent during the long dwell.

This slide represents the pattern of disappearance of dextrose from the abdominal cavity after installation, and it is expressed in percent remaining within the abdominal cavity from time zero when the solution is instilled. And the middle line, the red line represents the mean of 1,200 patients that we have studied, and you can see that there is a very rapid dissipation of the dextrose from the abdominal cavity, and that by two hours, less than 60 percent of dextrose remains in the abdominal cavity, and by four hours, less than 40 percent of dextrose remains in the abdominal cavity.

So the primary agent that is responsible for volume removal and ultra filtration in peritoneal dialysis dissipates because of a process of reabsorption.

Of equal importance to this matter is the fact that there is also a wide spread of values in the population, and patients, more than 50 percent of patients have a pattern of dissipation that is even

more severe than that observed in the mean. These patients we usually label as high and high average transporters, reflecting the avidity of reabsorption of dextrose from the abdominal cavity.

Now, this pattern of reabsorption of dextrose has functional implications on fluid removal during a peritoneal dialysis dwell. There are several opposing forces that are acting in the peritoneal cavity during peritoneal dialysis. One force that is continuously present and that is directed at removing fluid from the peritoneal cavity and the absorption of fluid back into the vascular system is the process of lymphatic and tissue absorption. This is a process that is continuous. It is not affected by the transport characteristics of the patient or any other parameter besides posture (phonetic) that we can identify, and this is a process that works against the therapeutic aim of removing fluid from the abdominal cavity.

The process that is moved by dextrose is represented in the yellow line, and this line represents the cumulative amount of fluid that enters

the abdominal cavity under the osmotic effect of dextrose, and initially you can see that there is a rapid entry of fluid into the peritoneal cavity under the effect of dextrose, and what we are showing here is the net fluid that enters the cavity.

So by one hour we have a significant amount of fluid that enters the abdominal cavity, but this pattern tends to plateau, and after two hours, very little further fluid enters the abdominal cavity under the effect of dextrose.

Now, if you relate this graph to the one I showed you just on the preceding slide, by two hours is the time when we have had close to 45 to 50 percent dissipation of the glucose concentrations within the peritoneal cavity. So there is parallelism between the therapeutic efficacy and the disappearance of the dextrose gradient.

Now, the summation of the effect of dextrose and the opposing force of lymphatic and tissue absorption give the green line, which is really what is observed therapeutically. That is, this green line represents the amount of fluid that the dialysis

process can remove from the patient's system if the abdominal cavity is drained at these particular time points.

Of importance is that after two hours, this line tends to have a downward slope because the entry of fluid into the peritoneal cavity kind of seizes or becomes at the very low rate, whereas removal of fluid from the peritoneal cavity is continuous. So this process after two hours tends to dominate the kinetic pattern of fluid in the cavity.

And this is represented here for a longer duration of dwell. The previous slide was up to four hours, but since we are going to discuss the efficacy of the new solution for the long dwell, these curves represent what happens over that time period.

And we are also illustrating here the impact of the different concentrations of dextrose. While increasing the concentration of dextrose progressively increases the amount of fluid that enters the peritoneal cavity, a pattern that is consistent for all three concentrations is the temporal decline after prolonged residence in the

abdominal cavity because the dextrose gradient is going to dissipate no matter what the initial concentration.

What distinguishes the three curves is the magnitude of the initial ultra filtration that can be achieved, and it is this initial magnitude that determines whether later on these curves will cross the zero line.

Now, once these curves cross the zero line, it means that more fluid has been removed from the peritoneal cavity than has entered the cavity. So in effect, the patient would be absorbing the peritoneal dialysis solution and gaining fluid rather than having the therapeutic effect of fluid removal.

Another pertinent aspect to mention here is that the amount of fluid that enters the cavity with 4.25 percent dextrose is quite significant, and this curve represents the mean value for the population, and you can see that it is up to one liter by four to six hours.

Now, this is added to the two to two and a half liters that the patient would have instilled in

their abdomen, and this results in significant abdominal distention, and it is not uncommon for patients to complain of abdominal distention because of this rapid and significant ultrafiltration.

Another factor I'd like to mention at this point is that these curves represent the means of the populations, but there are patients, particularly the high and high average transporters where these curves may be shifted downward because the reabsorption of glucose is much more avid in those groups of patients that constitute around 55 percent of the population. so their curves would lie below these average values for the group.

The utilization of 4.25 percent dextrose while resulting in very effective ultra filtration has also some other consequences. It does result in transient hyperglycemia in the dialysis patients, a hyperglycemia that can persist up to three hours with 4.25 percent dextrose, and this is paralleled also by hyper insulinemia in these patients that follows the same time pattern.

Now, Icodextrin, in contradistinction

because of its molecular size, has different intraperitoneal kinetics, and these are represented on this slide. The red line is from the earlier curve where I showed you the disappearance curve for dextrose, and the yellow line represents the mean values for Icodextrin rom our pharmacokinetic study.

And you can see that while for dextrose at two hours more than 40 percent has dissipated and by four hours only around 40 percent remain, with Icodextrin the osmotic agent continues to be present in significant concentrations in the peritoneal cavity, and at 12 hours, we have 60 percent that remains in the peritoneal cavity contrasted to dextrose where the 60 percent is crossed by two hours.

So the residence of the polymer in the peritoneal cavity is more prolonged, and hence, this is the underlying major mechanism for its effectiveness during the long dwell.

Now, of course, some Icodextrin is absorbed from the peritoneal cavity during the long dwell, and this absorption of the polymer does result in increased blood level of carbohydrates, and you can

see here from our 035 study, which was in patients on automated peritoneal dialysis where the duration of the dwell was between 12 to 16 hours, but the level of carbohydrates in the blood, total carbohydrates rises and remains stable for the duration of observation.

This slide illustrates these values in a 12-week study, but we have data from a one year and a two year study, and they show that the steady state achieved during the early phase of administration is maintained constant during prolonged administration as well.

On withdrawal of the solution, the levels of carbohydrate fall back to pre-administration levels in the blood.

One of the metabolites, intermediate metabolites of Icodextrin is maltose and the concentrations of maltose also rise, and they reach a steady state and then decline after the agent is withdrawn back to baseline levels.

The contrasting peritoneal kinetics of dextrose and Icodextrin are also reflected in the resultant ultra filtration. The dextrose curves are

the same curves I showed you on the previous slide, and what we have overlain here on the slide is the effect of Icodextrin.

And while with the dextrose concentrations, the various dextrose concentrations ultra filtration is fast and early and then characterized by a temporal decline during the long dwell, the effect of Icodextrin is sustained and gradual, and by the time you reach the duration of the long dwell, which is between eight to 16 hours, the values for Icodextrin become significantly higher as far as net ultra filtration to those achieved with 2.5 percent dextrose and 1.5 percent dextrose and become very similar to those achieved with 4.25 percent dextrose in the green cuff (phonetic).

This similarity between Icodextrin and 4.25 percent dextrose is achieved by different mechanisms. While 4.25 percent dextrose requires very rapid and significant initial ultra filtration followed by a decline so there is a fluctuation in intraperitoneal volume and intraperitoneal pressure, the changes with Icodextrin are more gradual and

sustained.

So both of these solutions give us similar net ultra filtration at the end, but we reach that endpoint by different mechanisms.

Also, with Icodextrin, plasma glucose remains constant and plasma insulin remains constant. So we do not have the transient hyperglycemia that we have seen on an earlier slide with dextrose or the transient type of insulinemia seen with 4.25 percent dextrose.

So in summary, Mr. Chairman, fluid management in PD patients is constrained by the nature of the underlying disease and by the limitations of the therapy that is offered these patients, particularly with the dextrose based solutions. So we have identified an unmet clinical need in this population.

There are clinical studies in the literature that suggest that outcome in this population is linked to the fluid management and the ability to control fluid in the population.

Extraneal, because of the nature of its

osmotic agent, is very successful during the long dwell and suited for that purpose specifically, and we believe can contribute significantly to fluid management in this population.

Now, to further explore this point, we have performed several clinical studies, and at this point I would like to invite our Vice President of Clinical Affairs, Dr. Marsha Wolfson, to present these trials to you.

CHAIRMAN BORER: Thank you very much, Dr. Mujais.

Are there any questions from the panel at this point?

(No response.)

CHAIRMAN BORER: No? Okay. Let's move right ahead then.

Thank you.

DR. WOLFSON: Thank you, Mr. Chairman.

And I'd like to share with you the results of our clinical trial experience with Extraneal. I'm going to first discuss our efficacy data, which will describe our net ultra filtration, the small solute

clearance of creatinine and urea during the long dwell, and some special assessments that we carried out in our long term, one year study, Study 131.

I'm then going to turn to the safety profile of Extraneal and describe our database. Dr. Ogrinc is going to discuss some statistical analyses on our observational mortality data through these studies, and I'll return to discuss adverse events and laboratory values.

Three key studies comprise our efficacy data, and I'm going to discuss these separately because they differed slightly in design. One was double blind and two were open label.

Two of them used 2.5 percent dextrose as a comparator and one evaluated 1.5, 2.5 and 4.25 percent dextrose.

Patients were on different dialysis delivery systems. Two studies evaluated Extraneal in comparison to dextrose solutions in CAPD patients who carry out manual exchanges during the day and have one long overnight dwell at night, and one of the studies evaluated automated peritoneal dialysis during which

patients had a cycler to deliver the therapy during the night and have a long daytime dwell.

I'm also going to describe some special assessments that we were able to carry out in our long term 131 study, which was primarily designed to observe safety over a one year period.

Two hundred and seven control patients and 216 Extraneal patients comprise our efficacy database. One hundred and twelve control and 175 patients also contributed to the assessments carried out in Study 131. One hundred and twenty-nine of those patients came from our 130 study.

Our 131 study was also double blind, and both APD and CAPD patients were included.

There were also five supportive studies, and the 28 control and 102 Extraneal patients in those studies contributed to our safety database.

There were no differences at baseline between the two groups in age, gender or race. There were also no differences in the causes of underlying end stage renal disease between the two groups, and the study population was representative of a

peritoneal dialysis population.

I'd like to turn to our primary endpoint, net ultra filtration. As Dr. Mujais described, net ultra filtration is the difference in volume obtained at the end of the long dwell from the amount of fluid infused at the start of that dwell.

In our 130 CAPD study, there was significant improvement in fluid removal during the long dwell as compared to baseline and as compared to the control group with Extraneal. This data is similar to the data we obtained in our Extraneal 035 study where once again we see significant improvement in net ultra filtration with Extraneal compared to both baseline and to the control group.

In this study, when patients were returned to the control two and a half percent dextrose solution during the follow-up period, net ultra filtration returned to the baseline level.

In the Midas study, which looked at both eight and 12 hour dwells compared to one and a half percent dextrose, mean net UF was again significantly improved with Extraneal at both eight and 12 hours

compared to baseline and compared to the control group.

When Extraneal was compared to the 4.25 percent dextrose solution in the same study at both eight and 12 hours, there were no statistically significant differences between the two groups in net ultra filtration.

We also wanted to examine the percentage of patients with negative ultra filtration. As Dr. Mujais explained, negative net ultra filtration means that less fluid is obtained at the end of the long dwell than what was instilled at the beginning of that dwell and represents fluid reabsorption.

During the CAPD study, approximately 20 percent of patients at baseline demonstrated negative net ultra filtration. Patients on Extraneal had a significant reduction in the percentage of patients displaying negative net ultra filtration during that study, and by week four virtually no patient had negative net ultra filtration.

And once again, we see very similar data in our APD study. At baseline in this longer daytime

dwell, over 70 percent of patients had fluid reabsorption during the long dwell.

During the study, again, there was significant reduction in the percentage of patients with fluid reabsorption when they were treated with Extraneal, and when they returned to their baseline two and a half percent dextrose solution, the percentage of patients with fluid reabsorption during the long dwell returned to the baseline level.

During the Midas study with one a half percent dextrose at both the eight and 12 hour dwell, again, there was significant reductions in the percentage of patients with negative net ultra filtration when they were treated with Extraneal as compared to the control group.

And in the same study, when the comparator was 4.25 percent dextrose, although there were no statistically significant differences in the percentage of patients with negative net ultra filtration in either group, there were numerically fewer patients with negative net ultra filtration in the Extraneal group as compared to the control group.

We also looked at the secondary endpoints of peritoneal creatinine and urea clearance. I'm only going to show you the data from one study in the interest of time because the data is similar to the APD study in which this was also studied.

There was significant increased creatinine and urea clearance during the long dwell with Extraneal as compared to the control group.

During a long term, one year safety Study 131, we had the opportunity to evaluate some other aspects of the management of patients with end stage renal disease treated with peritoneal dialysis. We evaluated edema, body weight, and quality of life, and I'd like to discuss edema first.

We decided to monitor peripheral edema in a more structured fashion.

Would you go back to the previous slide?

And we asked that the patients be assessed by the same individual over the course of the study. If edema was between zero and three plus, it was to be reported on a case report form. If edema was rated as four plus, it was to be recorded as an adverse event.

There was significantly less adverse events for peripheral edema in the Extraneal group, about six percent compared to almost 18 percent in the control group, and adverse events for other types of edema, such as generalized edema or facial edema were also lower with Extraneal compared to control.

We also took the opportunity during this long term, one year study to evaluate changes in body weight. Body weight is a very important parameter and is usually measured at every dialysis clinic visit in patients with end stage renal disease.

In the short term, changes in body weight reflect changes in fluid balance. However, in the long term, changes in body weight in dialysis patients reflect changes in body composition.

We asked that sites indicate whether patients were weighed during their dwell or before drain or after drain because of the continuous nature of the therapy in this long term study. Over the one year, patients treated with Extraneal maintained their body weight at 52 weeks with very little change. However, control patients gained an average of two

kilograms at 52 weeks, and this difference was statistically significant.

This is an interesting finding in view of the fact that in longitudinal studies of body composition in peritoneal dialysis patients, it has been reported that body weight increases due to an increase in body fat. This increase in body fat is felt to be related to the glucose load that patients receive in conjunction with their peritoneal dialysis therapy.

We also took the opportunity in this study to make some assessment and explore whether there was an impact on qualify of life over time. We didn't implement the KDQOL quality of life instrument at the start of this study, but rather was added as a late amendment, and so not all patients were able to complete both baseline in week 52.

In addition, because quality of life was not a primary endpoint in this study, it wasn't necessarily powered to determine differences in quality of life.

Patients were queried on 35 kidney

specific symptoms and problems in the short Form 36, and there were not statistically significant differences in quality of life between the two groups.

However, there were some interesting findings that I would like to share with you. For one thing, as you can notice, quality of life generally declined in both groups over this one-year study, and that isn't too surprising given the chronic nature of the disease.

There were some results favoring Extraneal. There were four of them that favored Extraneal and one favored dextrose solutions during the study.

In the 35 symptoms and problems, ten favored Extraneal and five favored dextrose, but overall there were no statistically significant differences.

However, in the health transition question asking patients to compare their health at the end of one year compared to baseline, 30 percent of the Extraneal patients versus four percent of the control patients reported that their health was much better as

compared to one year ago, and this difference was statistically significant.

So just to summarize the efficacy portion of my presentation, Extraneal provides superior ultra filtration compared to 1.5 or 2.5 percent dextrose, with comparable ultra filtration when compared to 4.25 percent dextrose.

Extraneal was also associated with a significant reduction in the number of patients with fluid reabsorption during the long dwell compared to both 1.5 and 2.5 percent dextrose with, again, comparability to 4.25 percent dextrose.

With Extraneal there's also a significantly increased peritoneal clearance of both urea and creatinine compared to 2.5 percent dextrose, and with Extraneal there's a potential benefit in preventing weight gain and edema and improving quality of life.

I'd like to turn now to the safety profile of Extraneal and first discuss the database. Eighty hundred and forty total patients, 347 in control, and 493 Extraneal patients comprise our safety database.

This is the largest database ever presented for approval of a peritoneal dialysis solution.

Control patients were exposed for a slightly shorter duration than Extraneal patients. Extraneal patients were exposed for 232 and a half days on average, with 215 Extraneal patients exposed greater than six months and 155 Extraneal patients exposed for greater than 12 months.

As you can see, most of the patients in both groups completed the studies, and there were no differences in the reasons for discontinuation in either group.

I'd like to turn now to Dr. Fran Ogrinc, our statistician, who is going to describe for you some of the statistical analyses that were carried out on the mortality data that we observed during these clinical trials.

DR. OGRINC: Thank you, Dr. Wolfson.

I'd first like to look at the Study 131, our long term U.S. safety study, and the original protocol called that each patient would be followed for 12 months of study completion or until dropout,

and then once discontinued the patient would be followed for an additional 30 days to collect safety issues related to adverse events, including death.

Now, the numbers here reflect the information that was collected using that data collection. There are no statistical differences between these numbers.

Now, based on information or guidance we received from a closed Advisory Committee last fall, Baxter initiated collection of follow-up data from the sites for those patients who had not completed the study and had not died. And the goal of this was to collect complete 13 month information on those patients, and in order to do that each site was contacted for those patients who met the criteria of not having died and not having completed the 12 month study.

And they were asked to provide the patient status, dead or alive, on 395 days after enrollment. These numbers here, including the 12 month mortality rates estimated from the Kaplan-Meier curve, were not statistically different.

All of our analyses then used these full 13 month data, including this Kaplan-Meier curve which shows comparable survival over time up to day 395, and again, no statistical differences were observed from log rank tests.

In order to more fully understand the mortality experience from our database, we pooled all of our studies together in order to come up with an overall assessment of mortality from those studies. This analysis used intent to treat methods during which each patient was followed until any death that was made known to us.

So some of these included deaths that were after study participation.

There are 46 deaths recorded in this table, and the total patient follow-up for Extraneal is 244 patient-years. The deaths per 1,000 patient-years are very comparable, as shown here, and of course there were no statistical differences.

If we estimate some of the death rates using the Kaplan-Meier estimation, we see the 12 month is very similar to what we saw for Study 131, and then

these longer term studies provided estimates at months 18 and 24, as well, where we see the improvement in the ratio of the death rates, and that information is reflected in the Kaplan-Meier curve shown here where we see the separation beyond one year of the curves.

So to summarize the mortality information, we combine data from all clinical studies to better describe the experience with Extraneal. This resulted in 366 Extraneal patients, with 244 patient-years of exposure to the product.

Survival times were comparable for controlled and Extraneal with a hazard ratio of approximately one. Ninety percent confidence intervals are also shown here.

Thank you.

CHAIRMAN BORER: Just at this point are there any specific questions the committee has with regard to the data we've been shown?

Tom.

DR. FLEMING: Let me just begin with one quick question about the mortality follow-up. I am pleased that you pursued a more complete and more

uniform follow-up. At least it looked like over approximately a year on the 131 patients, the 175 and 112.

DR. OGRINC: Correct.

DR. FLEMING: In fact, that gave us a number of additional events, a number of additional deaths.

One of the concerns or questions that I have is now as we go to the broader data set, recognizing that in the updated data set on 131, the 30-day deaths were 13 versus five, and then you improved the follow-up to more uniformity looking out at a year. That led to a total, I think, by two different approaches of 20 versus nine and 22 versus 12.

So in a sense, not enhanced excess deaths, but when you get more complete follow-up, the excess number of deaths stayed at eight.

Then as you go to the inclusion of the Midas and pro renal and Diana data sets, you come out with estimated hazard ratios of 1.03 or an estimated almost equivalent death rate of seven percent.

But a huge question is the data that was pooled in that analysis of the 366 versus the 285 included what I assumed to be more uniformly followed people in 131, but more sporadically followed people in the Midas, pro renal, and Diana.

Is that true, or is it actually true that you have now gone back and done a much more informative, consistent follow-up on survival through a uniform period of time in all of these patients?

And if not, the last part of the question is why not because that certainly would give us a much more reliable sense.

DR. OGRINC: You are correct. Study 131 is more uniform than the other studies, and those were older studies conducted by ML Laboratories, and it would be impossible to follow up on those patients at this point.

AUDIENCE MEMBER: If I could add something here, the evidence is that getting extended follow-up suggests that there wasn't a bias from not having it. All you did was get more information along the same lines of what you already had.

So the suggestion would be in the other studies not having that data doesn't mean that you have a bias. It just means that you have less information than you would like to have ideally.

DR. FLEMING: You say it's impossible. Can you clarify? Essentially, one of the advantages of a death endpoint is that it gives us at least a reasonable chance; we have epidemiological experts who are wonderful in their ability to be able to track patients.

It's awfully difficult in retrospect to get specific disease progression assessments that were missed, but survival status ought to be something, I think, we could retrospectively capture.

Can you clarify why you say it's impossible?

DR. OGRINC: It would be very difficult. It involves studies in the United Kingdom that were concluded seven, eight years ago and issues like that. You're correct. It's probably possible using death records, but it would be very difficult.

CHAIRMAN BORER: Okay. Are there any

other issues that anyone wants clarification on at this point? Paul.

DR. ARMSTRONG: Jeff, I wonder if we could get some better understanding of the quality of life presentation. There were a series of measurements, not all of which were directionally similar, and I didn't understand what they were nor whether we should put equal weighting to the various components.

That was, I think, slide 50 of the presentation. I would like some clarification on that, please.

DR. WOLFSON: Well, I think that there were no statistically significant differences. So I'm not sure that there is -- you know, there's just a trend here, not really any specific direction for any particular domain.

DR. ARMSTRONG: Perhaps you'd be good enough to explain what they are and --

DR. WOLFSON: Oh, sure. I'm sorry. I'm sorry.

DR. ARMSTRONG: -- the relative value.

DR. WOLFSON: There was no difference in

the physical functions domain. There was an advantage for Extraneal in the role of physical domain, the bodily pain domain, and the general health domain. There was an advantage for dextrose in the vitality domain. No difference in the social functioning, and an advantage for Extraneal in the role emotional. No difference in the mental health domains.

DR. ARMSTRONG: And my second question, Mr. Chairman, was there appears to be a different trend in the death rates as one looks over time, and I wondered if relative to the presentation on slide 61, whether we could learn anything about the cause of death and the time course in the two groups.

DR. WOLFSON: Can we have the slide on cause of death?

DR. ARMSTRONG: You're showing a 1.3 hazard ratio for Extraneal by month 12 and then a reversal of that that's quite striking thereafter, and I just wonder if we could get some more insight into the causes of death in the time course.

DR. WOLFSON: Can you show me the overall causes of death?

Thank you.

DR. OGRINC: I think we need to make an interjection here, going back to that other slide of the survival rates. Those rates beyond 12 months are a much smaller sample size. So you don't want to put too much credence in that, to be really honest with you. It's very intriguing evidence that there might be something beyond 12 months, but there's no feeling that that's been established.

DR. ARMSTRONG: I appreciate that clarification. Perhaps you'd be good enough to tell us what sample size we are working from then so that the denominators are clear because they're not clear to me.

DR. FLEMMING: Paul, my sense is, and my sense may not be right, but your question, I think, is very relevant, and it's related to my first concern. My sense is, and the sponsor can clarify if this is right, the 131 patients that make up 175 and 112 of these 366 and 285 were relatively uniformly followed through that year of about a year time period that Peter is referring to as being more reliable,

where as the other sources of data that came from the Midas, the pro renal, and the Diana I'm assuming were actually probably followed for the time periods of those studies, which were more along the lines of six months, 16 weeks, and four weeks.

DR. ARMSTRONG: It was mainly the Diana study. It was a two year study.

DR. FLEMMING: That's 16 weeks.

DR. OGRINC: The slide up there now shows you the actual sample sizes, and as you can see, there are 270 patients still remaining at 12 months, and then beyond 15 months it's 28 patients, and as Peter said, primarily from Diana, although there were some 131 patients who had information available that late because we included all deaths made known to us whether they were within 395 or beyond.

DR. ARMSTRONG: So warming to the task, Mr. Chairman, then in the first six months we see 15 deaths in the Extraneal group and five in the control group. So I'd be particularly interested in knowing whether the causes of death in that first six months were different than the cause of death thereafter.

DR. OGRINC: There were different sample sizes remember. There are always more Extraneal patients in these studies.

DR. ARMSTRONG: Fifteen out of 154, five out 134, correct?

DR. OGRINC: No, it's 15 out of the total. So it's 15 out of 169, and five out of 139.

DR. HIRSCH: What does that --

DR. OGRINC: Oh, I'm sorry. Censor means they were still alive in the analysis.

DR. ARMSTRONG: So we add 15.

DR. OGRINC: Plus 154.

DR. ARMSTRONG: Plus 154 to get the true denominator.

DR. OGRINC: Correct, for that interval.

DR. ARMSTRONG: All right. That notwithstanding, can we understand what the causes of death were in the first six months as opposed to thereafter? Is there some help we could get with that?

DR. WOLFSON: Do you want to see the causes of death?

DR. ARMSTRONG: Yes.

DR. WOLFSON: Can you please show the causes of death, please?

DR. FLEMMING: This is such an important slide. Just to follow up with Paul's questioning before we go to cause of death, essentially what we see is a total of 26 versus 20. The concern is that there is much more erratic follow-up as you get out certainly past six months and for sure past 12 months.

So in a certain sense the most unbiased assessments would be the shortest term assessment, and what this slide is suggesting is that over the first six months where we have the most complete follow-up, there is some evidence, not proven, but there is some evidence for potential excess in mortality.

It does lead me to be very interested in knowing what -- at least if we said through a 12 month time period -- what would be the overall relative mortality if we had more complete uniform follow-up through 12 months.

As you go from six to 12 months, that data is fairly complete from 131, but it's now much more